

Applicant: Jingyue Ju et al.  
U.S. Serial No.: 09/823,181  
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**Obviousness-Type Double Patenting Rejection**

In the March 4, 2003 Office Action, the Examiner stated that claims 74-92 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,046,005 in view of Arbo et al. (International Journal of Peptide and Protein Research, (1993), Vol. 42, pages 138-154) further in view of Liu et al. (Anal. Chem. (2000), Vol. 72, pages 33030-3310).

The Examiner stated that claims 1-22 of U.S. Patent No. 6,046,005 disclose basically and fundamentally the same method of instant claims 74-92, for sequencing DNA by detecting the identity of a dideoxynucleotide incorporated at the 3' end of a DNA sequencing fragment using mass spectrometry. The Examiner further stated that the basic steps of detection of DNA of instant claims are same as claims 1-22 of U.S. Patent No. 6,046,005, which comprises a) attaching a chemical moiety via a linker to a dideoxynucleotide; b) terminating a DNA sequencing reaction with the labeled dideoxynucleotide; c) capturing the labeled DNA sequencing fragment on a solid surface; d) washing the surface; e) freeing the DNA sequencing fragment from the surface; and f) analyzing using mass spectrometry so as to sequence the DNA.

The Examiner stated that claims 1-22 of U.S. Patent No. 6,046,005 do not teach a method, wherein the cleavable linkers are derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74, but that Arbo et al. teach a method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74 (Abstract and page 149, column 2 to page 151, column 1). The Examiner stated that it would have

been *prima facie* obvious to one having ordinary skill in the art at that time the invention was made to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in the claims 1-22 of U.S. Patent No. 6,046,005, in order to achieve the express advantages, as noted by U.S. Patent No. 6,046,005, of linkers which will comprise a cleavable moiety that is either photo or chemically cleavable.

The Examiner stated that U.S. Patent No. 6,046,005 in view of Arbo et al. do not teach the method, wherein the contacting is performed in a system comprising (i) a channel whose surface is coated with a compound that specifically interacts, with the chemically moiety, wherein the channel comprises a plurality of ends; (ii) a plurality of wells each suitable for holding a sample; (iii) a connection between each end of the channel and a well; and (iv) a means for moving the sample through the channel between wells. The Examiner also stated that Liu et al. teaches the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells (Abstract and Figures 1-3 and Experimental Section).

The Examiner stated that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the contacting is performed in a system comprising (i) a channel

whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends; (ii) a plurality of wells each suitable for holding a sample; (iii) a connection between each end of the channel and a well; and (iv) a means for moving the sample through the channel between wells of Liu et al. in the method of claims 1-22 of U.S. Patent No. 6,046,005 in view of Arbo et al., in order to achieve the express advantages, as noted by Liu et al., of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, and disposable device equipped with an independent electrospray exit port for each sample well, which represents an attractive alternative to FIA, and also of a device design, which demonstrates the potential of automated analysis.

In response, applicants respectfully traverse the Examiner's rejection.

Applicants assert that the invention claimed in the '005 patent in view of Arbo et al. and Liu et al. do not teach all the elements of the claimed invention. In particular, Arbo et al. does not teach a linker which is a derivative of 4-aminomethyl benzoic acid containing fluorine having a structure as set forth in claim 74. Moreover, the other references cited by the Examiner do not cure this deficiency.

Applicants further note that Arbo et al., contrary to the Examiner's assertion, does not teach a linker which is a derivative of 4-aminomethyl benzoic acid containing fluorine. Applicants assert that the TFMSA (trifluoromethane sulfonic acid) associated with the non-fluorine containing 4-aminomethyl benzoic

acid-based molecules shown in Arbo et al., (pages 149 to 150 cited by the Examiner), is in fact a "very weakly co-ordinating anion", (see page 140, first column).

In addition, applicants note that Liu et al. does not teach a channel whose surface is coated with a compound that specifically interacts with a chemical moiety, nor does it teach a channel connected to a well at each end, as cited in step (c) of claim 74. The remaining cited references do not cure this deficiency. Furthermore, Liu et al. does not teach step (e) of applicants' claim 74, namely releasing labeled DNA sequencing fragments from the surface (of the channel). The remaining cited references do not cure this deficiency. Thus, applicants' invention is not obvious over the claims of the '005 patent in view of Arbo et al. and Liu et al. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

**Rejection of Claims Under 35 U.S.C. §103(a)**

The Examiner stated that claims 74-92 are rejected under 35 U.S.C. §103(a) as being anticipated by Ju et al., U.S. Patent 6,046,005 (April 4, 2000) in view of Arbo et al. (International Journal of Peptide and Protein Research, (1993), Vol. 42, pages 138-154) further in view of Liu et al. (Anal. Chem. (2000), Vol. 72, pages 3303-3310). The Examiner stated that Ju et al. teach a method for sequencing DNA by detecting the identity of a single or plurality of dideoxynucleotide incorporated to the 3' end of a DNA sequencing fragment using mass spectrometry (Abstract and claims 1, 14, and 15, Figure 1 and Experimental Section), which comprises: a) attaching a chemical moiety via a linker to a dideoxynucleotide to produce a labeled dideoxynucleotide (claims

1 and 15); b) terminating a DNA sequencing reaction with the labeled dideoxynucleotide to generate a labeled DNA sequencing fragment having a 3' end and the chemical moiety is attached via the linker to the 3' end of the DNA sequencing fragment (claims 1 and 15 and Figure 1); c) capturing the labeled DNA sequencing fragment on a surface coated with a compound that specifically interacts with the chemical moiety attached via the linker to the DNA sequencing fragment, thereby capturing the DNA sequencing fragment (claims 1 and 15); d) washing the surface to remove any non-bound component (claims 1 and 15 and Experimental Section); e) freeing the DNA sequencing fragment from the surface by disrupting and cleaving the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment and the compound on the surface (claims 1 and 15 and Experimental Section and Figures 9-10); and f) analyzing the DNA sequencing fragment using mass spectrometry so as to sequence the DNA (claim 14). The Examiner further stated that Ju et al. teach a method wherein the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment and the compound on the surface comprises a biotin-streptavidin interaction (claims 19-20 and Experimental Section).

The Examiner also stated that Ju et al. teach a method, wherein the dideoxynucleotide comprises a cytosine or thymine with a 5-position and the linker to the DNA sequencing fragment and the compound on the surface comprises a biotin-streptavidin interaction (claims 19-20 and Experimental Section). The Examiner stated that Ju et al. teach a method, wherein a plurality of different linkers is used to increase mass separation between different labeled DNA sequencing fragments and thereby increase mass spectrometry resolution (column 7, lines 1-9 and column 9,

lines 15-32). The Examiner stated that Ju et al. teach a method, wherein the interaction of the linker is cleaved by ultraviolet light (Figures 9-10), and wherein the chemical moiety comprises biotin, the labeled dideoxynucleotide is a biotinylated dideoxynucleotide, and the surface is a streptavidin-coated magnetic bead solid surface (Figure 1 and Experimental Section and claim 20). The Examiner stated that Ju et al. teach a method, wherein the biotinylated dideoxynucleotide is selected from ddATP-11-biotin, ddCTP-11-biotin, ddGTP-11-biotin, ddTTP-11-biotin and the compounds of claims 67-70 (column 6, lines 35-64 and Figures 8-10).

The Examiner stated that Ju et al. teach a method, wherein any linker comprises a photo or chemically cleavable moiety, but do not teach a method wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74. The Examiner then stated that Arbo et al. teach method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74 (Abstract and page 149, Column 2 to page 151, Column 1).

The Examiner stated that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the chemically equivalent cleavable linkers, which are derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in the method of Ju et al., since Ju et al. state, "In such linkers, the linker will comprise a cleavable moiety that is either photo or chemically cleavable (Column 7, lines 1-3)." The Examiner stated that by employing scientific reasoning, an ordinary practitioner would have been motivated to combine and substitute the chemically

equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in the method of Ju et al., in order to achieve the express advantages, as noted by Ju et al., of linkers which will comprise a cleavable moiety that is either photo or chemically cleavable.

The Examiner stated that Ju et al. in view of Arbo et al. do not teach the method, wherein the contacting is performed in a system comprising (i) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends; (ii) a plurality of wells each suitable for holding a sample; (iii) a connection between each end of the channel and a well; and (iv) a means for moving the sample through channel between wells. The Examiner further stated that Liu et al. teaches the method, wherein the contacting is performed in a system comprising (i) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends; (ii) a plurality of wells each suitable for holding a sample; (iii) a connection between each end of the channel and a well; and (iv) a means for moving the sample through the channel between wells (Abstract and Figures 1-3 and Experimental Section).

The Examiner stated that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the contacting is performed in a system comprising (i) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety; wherein the channel comprises a plurality of ends; (ii) a plurality of wells each suitable for



holding a sample; (iii) a connection each end of the channel and a well; and (iv) a means for moving the sample through the channel between wells of Liu et al. in the method of Ju et al. in view of Arbo et al., since Liu et al. states, "Considering the wide acceptance of the of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, a disposable device equipped with an independent electrospray exit port for each sample well represents an attractive alternative to FIA (Page 3304, Column 1, lines 6-10)." The Examiner stated that Liu et al. provides further motivation as it states "Nevertheless, the model application demonstrates the potential of automated analysis with the present device design" (page 3309, column 1, last sentence of the second paragraph). An ordinary practitioner would have been motivated to combine and substitute the method, wherein the contacting is performed in a system comprising (i) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends; (ii) a plurality of wells each suitable for holding a sample; (iii) a connection between each end of the channel and a well; and (iv) a means for moving the sample through the channel between wells of Liu et al. in the method of Ju et al. in view of Arbo et al., in order to achieve the express advantages, as noted by Liu et al., of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, and disposable device equipped with an independent electrospray exit port for each sample well, which represents an attractive alternative to FIA, and also of a device design, which demonstrates the potential of automated analysis.

In response to the Examiner's rejection, applicants respectfully



traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants assert that the '005 patent, in view of Arbo et al. and Liu et al. do not teach all the elements of the claimed invention. In support of this position, applicants direct the Examiner to the discussion of the teachings of the '005 patent, Arbo et al. and Liu et al. set forth above in connection with the obviousness-type double patenting rejection.

Applicants maintain that the claimed invention is not obvious over the '005 patent, in view of Arbo et al. and Liu et al. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

#### Summary

Applicants maintain that the claims pending are in condition for allowance, and accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number

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provided below.

No fee is deemed necessary in connection with the filing of this Communication. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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6/4/03  
Date